American Journal of Hematology 54:329–331 (1997)

Treatment of Refractory Large Granular Lymphocytic Leukemia With 2-Chlorodeoxyadenosine

Martin J. Edelman,[1,2]* Robert T. O'Donnell,[1,2] and Ivan Meadows[1]

[1]VA Northern California Health Care System, Martinez, California
[2]University of California, Davis, Sacramento, California

A 50-year-old man with large granular lymphocytic leukemia (CD3+, CD8+) complicated by severe pancytopenia and life-threatening infections refractory to therapy with prednisone, methotrexate, cyclosporine, and G-CSF is described. Treatment with two cycles of 2-chlorodeoxyadenosine (2-CDA) at 0.1 mg/kg by continuous intravenous infusion for 7 days each cycle resulted in resolution of cytopenias and clearance of leukemic cells. T-cell receptor gene rearrangement, initially present, was not detectable after therapy with 2-CDA. The rapid and complete response to 2-CDA after unsuccessful attempts with prior therapy suggests that 2-CDA should be considered for initial treatment of this disorder. Am. J. Hematol. 54:329–331, 1997. © 1997 Wiley-Liss, Inc.

Key words: large granular lymphocytic leukemia; 2-chlorodeoxyadenosine

INTRODUCTION

Large granular lymphocytic (LGL) leukemia is a clonal T-cell disorder that may produce life-threatening cytopenias [1]. Despite responses to immunosuppressive agents such as prednisone and methotrexate, no therapy is standard. Recently, 2-chlorodeoxyadenosine (2-CDA, cladribine), a purine nucleoside analogue has become available that demonstrates activity in a wide range of lymphoproliferative disorders [2]. We report the first fully documented case of a complete response to 2-CDA in this disorder.

CASE REPORT

A 50-year-old Filipino man was referred for pancytopenia discovered during evaluation for mild fatigue and arthralgias. Complete blood count (CBC) demonstrated a white blood cell (WBC) count of 2,500/mm^3, with a differential of 2% neutrophils, 1% bands 93% lymphocytes, 2% atypical lymphpocytes, and 1% nucleated red blood cells (RBCs). Hemoglobin (Hb) was 11 g/dl, platelet count 119,000/mm^3. The peripheral smear demonstrated that approximately 50% of the WBCs were large granular lymphocytes with abundant cytoplasm and prominent azurophilic granules. The bone marrow biopsy was approximately 30% cellular with trilineal hypoplasia. The aspirate was hypocellular, with the myeloid series rarely showing differentiation beyond the promyelocyte stage; occasional large granular lymphocytes were seen. Tests for antinuclear antibodies, rheumatoid factor, complement, cryoglobulins were either negative or within normal limits. Two color flow cytometry of peripheral blood demonstrated an absolute increase of CD3/CD8+ lymphocytes (absolute count = 1,123/mm^3; normal range = 150–756) CD3/CD4+, CD16+ and CD56+ lymphocytes were within normal limits. A peripheral blood specimen showed clonal rearrangement of the T-cell receptor gene by Southern blot hybridization using a biotin-labeled probe to the joining (J-Beta-I/J-Beta-II) region (Specialty Laboratories, San Diego, CA).

The diagnosis of LGL leukemia was made based on the findings of pancytopenia with severe neutropenia, an increase of CD3/CD8+ LGLs, and evidence of clonal rearrangement of the T-cell receptor gene.

The patient remained stable for several months. He later developed pneumonitis and sepsis syndrome requiring hospital admission. A therapeutic trial was initiated with oral methotrexate (7.5 mg/m^2/week), prednisone (50

*Correspondence to: Martin J. Edelman, Division of Hematology/Oncology (111H), VA Northern California Health Care System, 150 Muir Road, Martinez, CA 94553.

Received 10 May 1996; Accepted 11 December 1996.

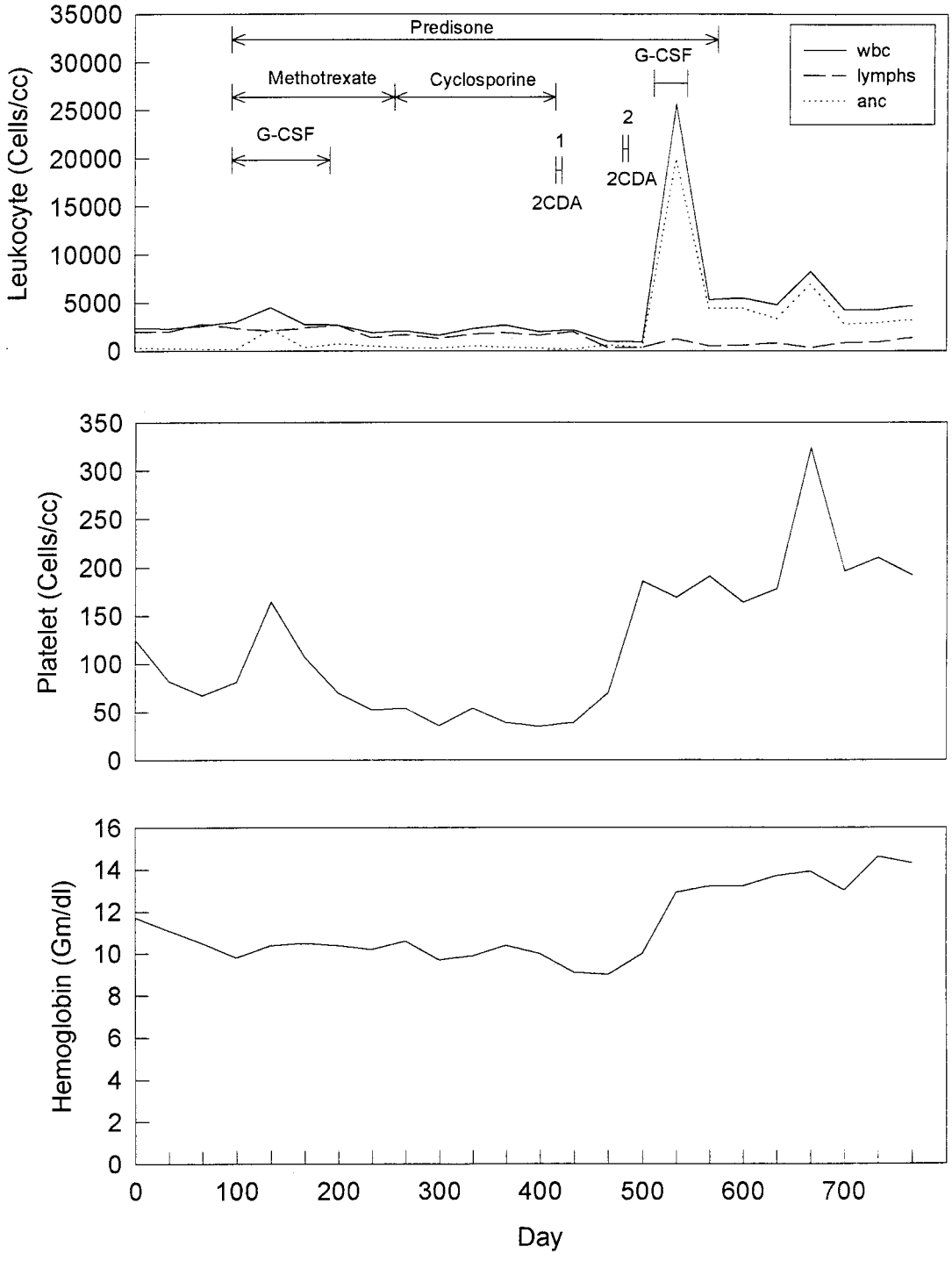

Fig. 1. Hematologic response to treatment.

mg/day) and granulocyte-colony-stimulating factor (G-CSF) (480 μg sc, tid), with minimal improvement (Fig. 1). He subsequently developed disseminated herpes zoster. Once the viral infection had resolved, a trial of cyclosporine at 200 mg bid (the most he could tolerate) was begun, also without effect. After obtaining informed consent, two cycles of 2-CDA were then administered at a dose of 0.1 mg/kg/day × 7 days by continuous intravenous infusion. The first cycle was complicated by culture-negative fever, which resolved after antibiotic therapy. After the second cycle, G-CSF (480 μg × 7 days sc) was administered, resulting in marked elevation of neutrophil counts (Fig. 1).

Prednisone was tapered and discontinued. Eight months after cessation of all therapy, the CBC demonstrated a WBC count of 4,800 (71% neutrophils), Hb of

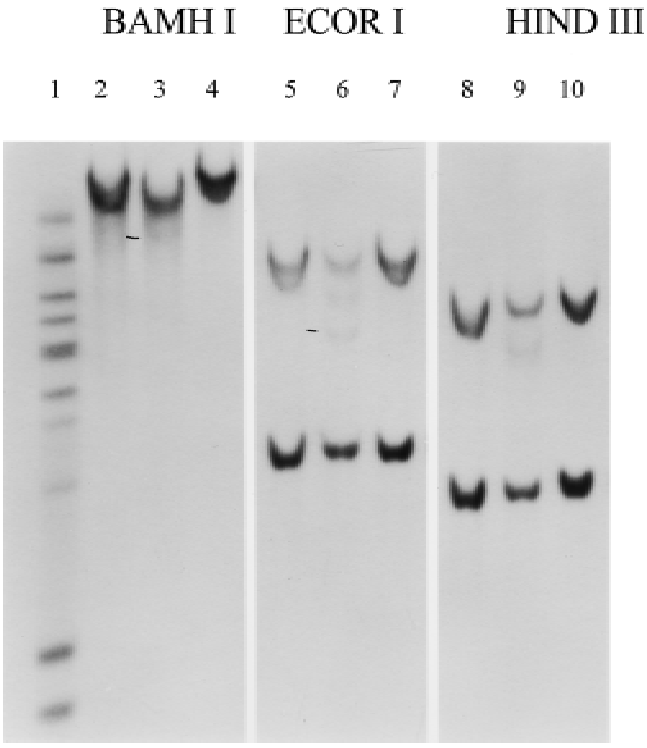

Fig. 2. T-cell receptor gene rearrangement studies. *Lane 1,* size marker; *lanes 2,5,8,* placental DNA; *lanes 3,6,9,* pre-therapy; *lanes 4,7,10,* post-therapy. Bars indicate rearranged bands. An additional 7.8-kb band seen in the *Eco*RI digest (*lane 6*) is probably an artifact.

14.2 g/dl, and a platelet count of 198,000/ml. LGLs were no longer seen in the peripheral blood. CD3+/CD8+ cells were 573/μl in the peripheral blood, within normal limits. T-cell gene rearrangement was no longer detectable (Fig. 2), and the bone marrow biopsy demonstrated 30–40% cellularity with normal trilineal maturation.

DISCUSSION

Although LGL leukemia is frequently described as an indolent disorder, profound neutropenia with consequent sepsis and death are frequent [1]. Treatment of the disorder is largely anecdotal and has consisted primarily of immunosuppressive regimens with prednisone [1], low-dose methotrexate [3], and cyclosporine [4]. G-CSF has also been used [5].

The largest reported experience is with low-dose oral methotrexate. Ten patients with severe neutropenia and LGL leukemia were treated by Loughran et al. [3]. Six of these patients responded with a mean time of 7.5 weeks. Two patients died early in the course of treatment due to sepsis.

Recently, a family of purine nucleoside analogues has become available with remarkable activity in low-grade lymphocytic malignancies [2]. 2-CDA, initially used in hairy cell leukemia, has also demonstrated activity in other low-grade B-cell malignancies. More recently, the drug has been successfully employed in T-cell lymphoproliferative diseases [5]. O'Brien et al. [5] reported two patients with LGL leukemia who achieved a complete remission, although the details of these cases regarding T-cell receptor rearrangement and prior therapy were not provided. Saven et al. [6] reported one partial response among four patients with LGL leukemia treated with 2-CDA. Two of these patients received only a single course of therapy, one having developed an aggressive lymphoma, the other postoperative complications from splenectomy [6]. Even including these patients, who may not have been fully evaluable, there are now a total of seven patients reported who have received 2-CDA for symptomatic LGL with four responders (3CR, 1PR). Furthermore, Mercieca et al. [7] reported 2CR in five patients with LGL treated with pentostatin, another purine nucleoside analogue, supporting the activity of this family of drugs in LGL.

The response of the patient described in this report, despite extensive and unsuccessful prior therapy, suggests a high level of activity for 2-CDA in LGL leukemia. The patient received concomitant prednisone, primarily because he was already receiving a prolonged course of steroid therapy and a rapid taper would have been injurious. We cannot exclude the possibility that there was a synergistic action of the two drugs. It is also possible that utilization of G-CSF after the second course of 2-CDA was important. The rapidity of response to treatment and ease of administration suggest that 2-CDA, possibly in combination with prednisone and G-CSF, should be considered as initial therapy for LGL leukemia complicated by life-threatening cytopenia.

ACKNOWLEDGMENT

The authors thank Frances Cinco-Hill for expert secretarial assistance.

REFERENCES

1. Loughran TP Jr: Clonal diseases of large granular lymphocytes. Blood 82:1, 1993.
2. Tallman MS, Hakimian D: Purine nucleoside analogs: Emerging roles in indolent lymphoproliferative disorders. Blood 86:7, 1995.
3. Loughran TP Jr, Kidd PG, Starkebaum G: Treatment of large granular lymphocyte leukemia with oral low-dose methotrexate. Blood 84:7, 1994.
4. Jakubowski A, Winton EF, Gencarelli A, Gabrilove J: Treatment of chronic neutropenia associated with large granular lymphocytosis with Cyclosporine A and Filgrastim. Am J Hematol 50:288–291, 1995.
5. O'Brien S, Kurzrock R, Duvic M, et al: 2-Chlorodeoxyadenosine therapy in patients with T-cell lymphoproliferative disorders. Blood 84:3, 1994.
6. Saven A, Tallman M, Hakimian D, et al: Treatment of large granular lymphocyte (LGL) leukemia with 2-chlorodeoxyadenosine (2-CdA). Proc Am Soc Clin Oncol 14:341, 1995 (abst 1027).
7. Mercieca J, Matutes E, Dearden C, MacLennan K, Catovsky D: The role of pentostatin in the treatment of T-cell malignancies: Analysis of response rate in 145 patients according to disease subtype. J Clin Oncol 12:2588–2593, 1994.

NOTE ADDED IN PROOF

The patient remains well and in complete hematologic remission 18 months after completion of therapy.